

Table 43 Organ weights of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control		1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene			
	0		45	180		720
Number of males	6		6	6		6
Body weight (g)	496 ± 34		494 ± 38	474 ± 24		446 ± 26 *
Brain (g)	2.05 ± 0.05		2.06 ± 0.06	2.11 ± 0.09		2.05 ± 0.07
	(g%)	0.41 ± 0.03	0.42 ± 0.03	0.45 ± 0.03		0.46 ± 0.03 *
Pituitary (mg)	14.3 ± 1.3		13.5 ± 1.3	15.3 ± 1.3		14.2 ± 1.5
	(mg%)	2.9 ± 0.2	2.8 ± 0.3	3.2 ± 0.3		3.2 ± 0.3
Thyroids (mg)	22.5 ± 4.7		23.7 ± 4.9	24.0 ± 2.6		29.1 ± 4.0 *
	(mg%)	4.5 ± 0.8	4.8 ± 1.1	5.1 ± 0.6		6.6 ± 1.0 **
Thymus (mg)	278 ± 41		270 ± 28	289 ± 53		265 ± 64
	(mg%)	56 ± 7	55 ± 6	61 ± 11		59 ± 12
Heart (g)	1.52 ± 0.13		1.54 ± 0.10	1.55 ± 0.14		1.44 ± 0.16
	(g%)	0.31 ± 0.02	0.31 ± 0.02	0.33 ± 0.02		0.32 ± 0.03
Liver (g)	13.26 ± 1.49		15.17 ± 1.37 *	17.22 ± 1.27 **		19.95 ± 0.64 **
	(g%)	2.67 ± 0.17	3.07 ± 0.22 *	3.64 ± 0.17 **		4.49 ± 0.34 **
Spleen (mg)	762 ± 129		665 ± 106	690 ± 81		735 ± 109
	(mg%)	153 ± 20	135 ± 22	146 ± 14		164 ± 20
Kidneys (g)	2.96 ± 0.20		3.02 ± 0.31	3.49 ± 0.34 **		3.49 ± 0.21 **
	(g%)	0.60 ± 0.03	0.61 ± 0.04	0.74 ± 0.06 **		0.78 ± 0.03 **
Adrenals (mg)	55.8 ± 8.2		63.4 ± 9.1	62.9 ± 8.2		58.8 ± 6.2
	(mg%)	11.3 ± 1.9	12.9 ± 1.7	13.2 ± 1.2		13.2 ± 1.4
Testes (g)	3.29 ± 0.17		3.44 ± 0.15	3.39 ± 0.34		3.41 ± 0.31
	(g%)	0.67 ± 0.05	0.70 ± 0.06	0.72 ± 0.07		0.77 ± 0.08 *
Epididymides (g)	1.21 ± 0.06		1.21 ± 0.12	1.21 ± 0.08		1.22 ± 0.06
	(g%)	0.25 ± 0.02	0.25 ± 0.04	0.25 ± 0.02		0.27 ± 0.02

Each value shows mean ± S.D.

Significantly different from control group (*: P<0.05, **: P<0.01).

Table 44 Organ weights of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of l,l'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	l,l'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene			
	Control 0	45	180	720
Number of females	11	12	10	9
Body weight (g)	279 ± 17	281 ± 14	273 ± 14	266 ± 13
Brain (g)	1.94 ± 0.04	1.92 ± 0.07	1.92 ± 0.06	1.87 ± 0.08
(g%)	0.70 ± 0.04	0.69 ± 0.04	0.71 ± 0.03	0.70 ± 0.04
Pituitary (mg)	15.1 ± 2.1	15.4 ± 2.0	14.3 ± 1.7	13.8 ± 2.4
(mg%)	5.4 ± 0.8	5.5 ± 0.8	5.3 ± 0.5	5.2 ± 0.7
Thyroids (mg)	15.8 ± 3.2	16.3 ± 2.3	18.4 ± 5.3	19.8 ± 3.6
(mg%)	5.7 ± 1.1	5.8 ± 1.0	6.8 ± 1.9	7.5 ± 1.6 *
Thymus (mg)	223 ± 39	243 ± 61	224 ± 46	236 ± 53
(mg%)	80 ± 15	87 ± 21	82 ± 16	89 ± 20
Heart (g)	1.00 ± 0.08	0.98 ± 0.06	0.95 ± 0.09	0.98 ± 0.07
(g%)	0.36 ± 0.02	0.35 ± 0.02	0.35 ± 0.03	0.37 ± 0.03
Liver (g)	9.13 ± 1.05	9.96 ± 0.47	11.48 ± 0.88 **	13.65 ± 1.51 **
(g%)	3.27 ± 0.26	3.55 ± 0.20	4.21 ± 0.27 **	5.14 ± 0.57 **
Spleen (mg)	626 ± 110	653 ± 132	672 ± 125	584 ± 86
(mg%)	223 ± 30	232 ± 45	246 ± 43	220 ± 31
Kidneys (g)	1.99 ± 0.28	2.00 ± 0.21	2.12 ± 0.19	2.05 ± 0.20
(g%)	0.71 ± 0.07	0.71 ± 0.07	0.78 ± 0.08	0.77 ± 0.07
Adrenals (mg)	74.4 ± 7.5	74.3 ± 6.4	71.9 ± 11.9	71.5 ± 7.8
(mg%)	26.7 ± 2.4	26.5 ± 2.7	26.4 ± 3.9	26.9 ± 2.7
Ovaries (mg)	99.7 ± 11.4	95.6 ± 6.6	95.7 ± 8.7	88.9 ± 10.3 *
(mg%)	35.8 ± 4.3	34.1 ± 2.9	35.2 ± 3.1	33.4 ± 2.7
Uterus (mg)	640 ± 139	607 ± 155	561 ± 77	518 ± 136
(mg%)	231 ± 59	218 ± 65	206 ± 31	196 ± 56

Each value shows mean ± S.D.

Significantly different from control group (*: P<0.05, **: P<0.01).

Table 45 Organ weights of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of l,l'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control		l,l'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene			
	0		45	180	720	
Number of males	6		6	6	6	
Body weight (g)	512 ± 15		519 ± 29	515 ± 28	478 ± 41	
Brain (g)	2.17 ± 0.09		2.08 ± 0.06	2.15 ± 0.12	2.07 ± 0.09	
(g%)	0.42 ± 0.02		0.40 ± 0.03	0.42 ± 0.03	0.43 ± 0.03	
Pituitary (mg)	14.5 ± 1.7		14.1 ± 1.7	13.8 ± 1.4	14.1 ± 1.0	
(mg%)	2.8 ± 0.3		2.7 ± 0.3	2.7 ± 0.1	2.9 ± 0.3	
Thyroids (mg)	18.6 ± 3.2		24.9 ± 4.7 *	20.0 ± 1.8	24.5 ± 4.4 *	
(mg%)	3.7 ± 0.6		4.8 ± 0.7 *	3.9 ± 0.4	5.2 ± 0.8 **	
Thymus (mg)	309 ± 91		266 ± 74	255 ± 48	287 ± 48	
(mg%)	61 ± 19		52 ± 16	49 ± 7	60 ± 10	
Heart (g)	1.58 ± 0.13		1.56 ± 0.11	1.63 ± 0.19	1.50 ± 0.14	
(g%)	0.31 ± 0.03		0.30 ± 0.03	0.32 ± 0.03	0.31 ± 0.02	
Liver (g)	12.23 ± 0.93		13.32 ± 1.57	13.59 ± 1.09	14.34 ± 2.39	
(g%)	2.38 ± 0.12		2.56 ± 0.17	2.64 ± 0.11	2.98 ± 0.29 **	
Spleen (mg)	771 ± 96		809 ± 128	760 ± 138	765 ± 117	
(mg%)	150 ± 19		156 ± 19	148 ± 23	160 ± 19	
Kidneys (g)	3.13 ± 0.18		3.16 ± 0.25	3.36 ± 0.30	3.36 ± 0.58	
(g%)	0.61 ± 0.03		0.61 ± 0.04	0.65 ± 0.04	0.70 ± 0.08 *	
Adrenals (mg)	61.3 ± 6.2		57.0 ± 9.9	58.3 ± 9.4	65.4 ± 11.2	
(mg%)	12.0 ± 1.3		11.1 ± 2.5	11.4 ± 1.7	13.6 ± 1.5	
Testes (g)	3.63 ± 0.20		3.40 ± 0.21	3.46 ± 0.27	3.44 ± 0.18	
(g%)	0.71 ± 0.05		0.66 ± 0.03	0.68 ± 0.08	0.72 ± 0.07	
Epididymides (g)	1.33 ± 0.15		1.36 ± 0.13	1.32 ± 0.11	1.30 ± 0.15	
(g%)	0.26 ± 0.03		0.26 ± 0.03	0.26 ± 0.04	0.27 ± 0.02	

Each value shows mean ± S.D.

Significantly different from control group (*: P<0.05, **: P<0.01).

Table 46 Organ weights of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control		1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene	
	0		180	720
Number of females	6		6	5
Body weight (g)	287 ± 15	272 ± 13	274 ± 15	
Brain (g)	1.95 ± 0.07	1.95 ± 0.07	1.97 ± 0.06	
	(g%)	0.68 ± 0.03	0.72 ± 0.05	0.72 ± 0.04
Pituitary (mg)	14.9 ± 2.2	18.1 ± 2.6	15.9 ± 2.0	
	(mg%)	5.2 ± 0.7	6.7 ± 1.2 *	5.8 ± 0.7
Thyroids (mg)	16.5 ± 3.5	14.9 ± 2.9	19.3 ± 2.9	
	(mg%)	5.7 ± 1.2	5.5 ± 1.1	7.0 ± 0.8
Thymus (mg)	256 ± 48	295 ± 55	285 ± 70	
	(mg%)	90 ± 20	109 ± 21	103 ± 21
Heart (g)	0.93 ± 0.07	0.90 ± 0.08	0.94 ± 0.01	
	(g%)	0.32 ± 0.03	0.33 ± 0.02	0.35 ± 0.02
Liver (g)	7.39 ± 0.79	7.22 ± 0.54	8.18 ± 0.58	
	(g%)	2.57 ± 0.20	2.66 ± 0.09	2.98 ± 0.10 **
Spleen (mg)	547 ± 61	511 ± 93	549 ± 89	
	(mg%)	191 ± 24	187 ± 29	200 ± 24
Kidneys (g)	1.84 ± 0.11	1.80 ± 0.18	1.90 ± 0.06	
	(g%)	0.64 ± 0.03	0.66 ± 0.04	0.70 ± 0.03 *
Adrenals (mg)	67.1 ± 6.8	66.0 ± 8.1	68.1 ± 9.9	
	(mg%)	23.4 ± 2.4	24.3 ± 2.7	24.8 ± 2.7
Ovaries (mg)	78.6 ± 11.7	82.3 ± 8.8	88.5 ± 9.9	
	(mg%)	27.4 ± 4.2	30.3 ± 2.7	32.3 ± 3.1
Uterus (mg)	637 ± 231	626 ± 200	566 ± 69	
	(mg%)	223 ± 87	229 ± 64	207 ± 30

Each value shows mean ± S.D.

Significantly different from control group (*: P<0.05, **: P<0.01).

Table 47 Histopathological findings of dead female rats in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene					
Grade	720					
Findings	N ^{a)}	A ^{b)}	±	+	2+	3+
Whole organs and tissues	[1] ^{c)}					
Postmortal change	0	1	0	1	0	0
Liver	[1]					
Swelling, hepatocyte, centrilobular	0	1	0	1	0	0

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, submandibular lymph node, mesenteric lymph node, kidney, urinary bladder, ovary, uterus, vagina, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum or femur), bone (sternum or femur), and mammary gland.

Table 48 Histopathological findings of dead female rats (recovery group) in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene					
mg/kg	720					
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+
Findings						
Whole organs and tissues	[1] ^{c)}					
Postmortal change	0	1	0	1	0	0
Liver	[1]					
Swelling, hepatocyte, centrilobular	0	1	0	1	0	0

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Examined heart, lung, trachea, liver, pancreas, sublingual gland, submandibular gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, thymus, spleen, submandibular lymph node, mesenteric lymph node, kidney, urinary bladder, ovary, uterus, vagina, pituitary, adrenal, thyroid, parathyroid, cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, eyeball, Harderian gland, bone marrow (sternum or femur), bone (sternum or femur), and mammary gland.

Table 49-1 Histopathological findings of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control						1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene																			
	0						45				180				720											
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+		
Findings																										
Heart	[6] ^{c)}						[0]						[0]						[6]							
Cellular infiltration	4	2	2	0	0	0													6	0	0	0	0	0	0	
Lung	[6]						[0]						[0]						[6]							
Mineralization, vascular wall	6	0	0	0	0	0													3	3	3	0	0	0	0	
Trachea	[6]						[0]						[0]						[6]							
Liver	[6]						[6]						[6]						[6]							
Swelling, hepatocyte, centrilobular	6	0	0	0	0	0	5	1	1	0	0	0	0	6	4	2	0	0	0	6	0	2	4	0	0	** ##
Basophilic change, hepatocyte	6	0	0	0	0	0	5	1	1	0	0	0	0	6	6	0	0	0	0	6	0	6	0	0	0	** ##
Necrosis, hepatocyte, focal	5	1	1	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	0	
Pancreas	[6]						[0]						[0]						[6]							
Sublingual gland	[6]						[0]						[0]						[6]							
Submandibular gland	[6]						[0]						[0]						[6]							
Esophagus	[6]						[0]						[0]						[6]							
Stomach	[6]						[0]						[0]						[6]							
Duodenum	[6]						[0]						[0]						[6]							
Jejunum	[6]						[0]						[0]						[6]							
Mineralization, Peyer's patch	5	1	1	0	0	0													4	2	2	0	0	0	0	
Ileum	[6]						[0]						[0]						[6]							
Cecum	[6]						[0]						[0]						[6]							
Colon	[6]						[0]						[0]						[6]							
Rectum	[6]						[0]						[0]						[6]							
Thymus	[6]						[0]						[0]						[6]							
Spleen	[6]						[0]						[0]						[6]							
Submandibular lymph node	[6]						[0]						[0]						[6]							
Mesenteric lymph node	[6]						[0]						[0]						[6]							
Kidney	[6]						[6]						[6]						[6]							
Hyaline droplet, tubular epithelium	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	3	3	3	0	0	0	0	* #
Degeneration, tubular epithelium	6	0	0	0	0	0	6	0	0	0	0	0	5	1	1	0	0	0	5	1	1	0	0	0	0	
Urinary bladder	[6]						[0]						[0]						[6]							

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Significantly different from control group (*: P<0.05, **: P<0.01).

Significantly different by dose response test (#: P<0.05, ##: P<0.01).

Table 49-2 Histopathological findings of male rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control						1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene																			
	0						45						180						720							
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+		
Findings																										
Testis	[6] ^{c)}						[0]						[0]						[6]							
Epididymis	[6]						[0]						[0]						[6]							
Seminal vesicle	[6]						[0]						[0]						[6]							
Prostate	[6]						[0]						[0]						[6]							
Cellular infiltration		3	3	0	0	0													6	0	0	0	0	0		
Pituitary	[6]						[0]						[0]						[6]							
Adrenal	[6]						[0]						[0]						[6]							
Thyroid	[6]						[6]						[6]						[6]							
Follicular cell hyperplasia, diffuse		4	2	1	1	0	0	5	1	1	0	0	0	3	3	2	1	0	0	0	6	1	5	0	0	*
Parathyroid	[5]						[0]						[0]						[6]							
Cerebrum	[6]						[0]						[0]						[6]							
Cerebellum	[6]						[0]						[0]						[6]							
Medulla oblongata	[6]						[0]						[0]						[6]							
Spinal cord	[6]						[0]						[0]						[6]							
Sciatic nerve	[6]						[0]						[0]						[6]							
Eyeball	[6]						[0]						[0]						[6]							
Harderian gland	[6]						[0]						[0]						[6]							
Bone marrow (sternum or femur)	[6]						[0]						[0]						[6]							
Bone (sternum or femur)	[6]						[0]						[0]						[6]							

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Significantly different from control group (*: P<0.05).

Table 50-1 Histopathological findings of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control					1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene																				
	0					45					180					720										
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+		
Findings																										
Heart	[6] ^{c)}						[0]						[0]						[6]							
Lung	[6]						[0]						[0]						[6]							
Trachea	[6]						[0]						[0]						[6]							
Liver	[6]						[6]						[6]						[6]							
Swelling, hepatocyte, centrilobular	6	0	0	0	0	0	6	0	0	0	0	0	0	6	6	0	0	0	0	6	6	0	0	0	0	** ##
Basophilic change, hepatocyte	6	0	0	0	0	0	6	0	0	0	0	0	0	6	6	0	0	0	0	6	6	0	0	0	0	** ##
Pancreas	[6]						[0]						[0]						[6]							
Sublingual gland	[6]						[0]						[0]						[6]							
Submandibular gland	[6]						[0]						[0]						[6]							
Esophagus	[6]						[0]						[0]						[6]							
Stomach	[6]						[0]						[0]						[6]							
Duodenum	[6]						[0]						[0]						[6]							
Jejunum	[6]						[0]						[0]						[6]							
Ileum	[6]						[0]						[0]						[6]							
Cecum	[6]						[0]						[0]						[6]							
Colon	[6]						[0]						[0]						[6]							
Rectum	[6]						[0]						[0]						[6]							
Thymus	[6]						[0]						[0]						[6]							
Spleen	[6]						[0]						[0]						[6]							
Hematopoiesis, extramedullary	3	3	3	0	0	0													2	4	4	0	0	0		
Submandibular lymph node	[6]						[0]						[0]						[6]							
Mesenteric lymph node	[6]						[0]						[0]						[6]							
Kidney	[6]						[6]						[6]						[6]							
Proliferation, collecting tubular epithelium	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	5	1	0	1	0	0		
Dilatation, urinary tubule	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	5	1	1	0	0	0		
Urinary bladder	[6]						[0]						[0]						[6]							

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Significantly different from control group (*: P<0.05, **: P<0.01).

Significantly different by dose response test (##: P<0.01).

Table 50-2 Histopathological findings of female rats on termination of administration period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control						1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene																		
	0						45						180						720						
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	
Findings																									
Ovary	[6] ^{c)}						[0]						[0]						[6]						
Uterus	[6]						[0]						[0]						[6]						
Vagina	[6]						[0]						[0]						[6]						
Pituitary	[6]						[0]						[0]						[6]						
Adrenal	[6]						[0]						[0]						[6]						
Thyroid	[6]						[6]						[6]						[6]						
Follicular cell hyperplasia, diffuse	6	0	0	0	0	0	4	2	2	0	0	0	5	1	1	0	0	0	3	3	3	0	0	0	0
Parathyroid	[6]						[0]						[0]						[6]						
Cerebrum	[6]						[0]						[0]						[6]						
Cerebellum	[6]						[0]						[0]						[6]						
Medulla oblongata	[6]						[0]						[0]						[6]						
Spinal cord	[6]						[0]						[0]						[6]						
Sciatic nerve	[6]						[0]						[0]						[6]						
Eyeball	[6]						[0]						[0]						[6]						
Harderian gland	[6]						[0]						[0]						[6]						
Bone marrow (sternum or femur)	[6]						[0]						[0]						[6]						
Bone (sternum or femur)	[6]						[0]						[0]						[6]						
Mammary gland	[6]						[0]						[0]						[6]						

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 51 Histopathological findings of male rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control						1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene																			
	0						45				180				720											
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+		
Findings	[6] ^{c)}						[6]						[6]						[6]							
Liver	[6] ^{c)}						[6]						[6]						[6]							
Swelling, hepatocyte, centrilobular	6	0	0	0	0	0	6	0	0	0	0	0	5	1	1	0	0	0	0	6	6	0	0	0	0	** ##
Adhesion	6	0	0	0	0	0	5	1	1	0	0	0	6	0	0	0	0	0	0	6	0	0	0	0	0	
Kidney	[6]						[6]						[6]						[6]							
Hyaline droplet, tubular epithelium	5	1	1	0	0	0	6	0	0	0	0	0	5	1	1	0	0	0	0	6	0	0	0	0	0	
Degeneration, tubular epithelium	6	0	0	0	0	0	6	0	0	0	0	0	6	0	0	0	0	0	0	5	1	1	0	0	0	
Thyroid	[6]						[6]						[6]						[6]							
Follicular cell hyperplasia, diffuse	6	0	0	0	0	0	5	1	1	0	0	0	4	2	2	0	0	0	0	3	3	3	0	0	0	
Ectopic, thymic tissue	6	0	0	0	0	0	5	1	1	0	0	0	6	0	0	0	0	0	0	6	0	0	0	0	0	

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of males examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Significantly different from control group (**: P<0.01).

Significantly different by dose response test (##: P<0.01).

Table 52 Histopathological findings of female rats on termination of recovery period in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control						1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene											
	0						180						720					
Grade	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+	N ^{a)}	A ^{b)}	±	+	2+	3+
Findings																		
Liver	[6] ^{c)}						[6]						[5]					
Swelling, hepatocyte, centrilobular	6	0	0	0	0	0	6	0	0	0	0	0	3	2	2	0	0	0
Kidney	[6]						[6]						[5]					
Cyst, left	6	0	0	0	0	0	5	1	1	0	0	0	5	0	0	0	0	0
Thyroid	[6]						[6]						[5]					

a): No abnormality detected.

b): Abnormality detected.

c): Number in brackets is number of females examined.

Grade of histopathological findings: ±: slight, +: mild, 2+: moderate, 3+: marked.

Table 53 Reproductive functions of male rats and female rats in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	Control	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene		
	0	45	180	720
mg/kg	0	45	180	720
Number of females	12	12	12	11
Number of estrous cases before pairing (14 days)				
Mean±S.D.	3.5 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	2.9 ± 0.8
Number of pairs	12	12	12	11
Number of pairs with successful copulation	12	12	12	11
Copulation index (%) ^{a)}	100.0	100.0	100.0	100.0
Number of conceiving days				
Mean±S.D.	2.8 ± 1.1	2.4 ± 1.3	3.8 ± 4.4	2.4 ± 1.3
Conceiving days 1-5	12	12	10	11
Conceiving days ≥6	0	0	2	0
Number of pregnant females	11	12	11	10
Fertility index (%) ^{b)}	91.7	100.0	91.7	90.9

a): (Number of pairs with successful copulation / number of pairs)×100.

b): (Number of pregnant females / number of pairs with successful copulation)×100.

Table 54 Observation of pups (F₁) in combined repeat dose and reproductive/development toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control		1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene					
	0		45		180		720	
Number of dams	11		12		11		10	
Length of gestation (days)	22.1 ± 0.3		22.1 ± 0.5		22.0 ± 0.0		22.5 ± 0.5	
Pregnancy days = 21	0		1		0		0	
Pregnancy days = 22	10		9		11		5	
Pregnancy days ≥ 23	1		2		0		5	
Corpora lutea	15.9 ± 1.7		14.7 ± 1.5		15.7 ± 1.1		12.2 ± 3.3 **	
Implantation scars	14.9 ± 1.6		14.1 ± 1.3		14.8 ± 1.2		9.1 ± 4.0 **	
Implantation index (%) ^{a)}	93.8 ± 4.8		96.2 ± 4.3		94.3 ± 5.0		74.1 ± 24.5	
Gestation index (%) ^{b)}	100.0		100.0		100.0		100.0	
Pups born	13.7 ± 2.0		13.4 ± 1.4		14.2 ± 1.1		8.0 ± 3.9 **	
Stillbirths	0.3 ± 0.5		0.2 ± 0.6		0.0 ± 0.0		0.8 ± 1.6	
Live pups born	13.5 ± 1.9		13.3 ± 1.7		14.2 ± 1.1		7.2 ± 3.6 **	
Sex ratio at birth ^{c)}	0.96 ± 0.35		1.00 ± 0.53		1.03 ± 0.56		1.13 ± 0.97	
(Total male/total female)	69/79		73/86		74/82		31/41	
Delivery index (%) ^{d)}	90.2 ± 6.3		94.2 ± 8.9		95.8 ± 4.4		79.9 ± 21.7	
Birth index (%) ^{e)}	90.4 ± 6.2		94.2 ± 9.0		95.8 ± 4.3		80.0 ± 21.6	
Live birth index (%) ^{f)}	98.2 ± 3.2		98.6 ± 4.9		100.0 ± 0.0		92.1 ± 15.1	
Live pups on Day 4 of lactation	13.4 ± 2.0		12.9 ± 1.8		12.8 ± 4.4		7.0 ± 3.9 **	
Sex ratio on Day 4 of lactation ^{c)}	0.94 ± 0.36		1.00 ± 0.53		1.01 ± 0.58 (10)		1.14 ± 1.03 (9)	
(Total male/total female)	68/79		71/84		66/75		30/40	
Viability index (%) ^{g)}	99.2 ± 2.5		97.4 ± 4.0		90.3 ± 30.0		90.0 ± 31.6	
External abnormalities (%) ^{h)}	0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0		0.0 ± 0.0	

Each value shows mean ± S.D. per dam.

Significantly different from control group (**: P<0.01).

Figures in parentheses indicate number of dams.

a): (Number of implantation scars/number of corpora lutea)×100.

c): Number of male pups/number of female pups.

e): (Number of live pups born/number of implantation scars)×100.

g): (Number of live pups on Day 4/number of live pups born)×100.

b): (Number of dams with live pups/number of pregnant dams)×100.

d): (Number of pups born/number of implantation scars)×100.

f): (Number of live pups born/number of pups born)×100.

h): (Number of pups with external abnormalities/number of live pups)×100.

Table 55 Delivery conditions and nursing conditions of dams in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	mg/kg	Number of dams and delivery conditions/nursing conditions	Delivery conditions	Nursing conditions				
				Days of lactation				
				0	1	2	3	4
Control	0	Number of dams	11	11	11	11	11	11
		Normal	11	11	11	11	11	11
1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene	45	Number of dams	12	12	12	12	12	12
		Normal	12	12	12	12	12	12
	180	Number of dams	11	11	11	11	11	10
		Normal	11	11	11	10	10	10
		Faulty nest-building	-	0	0	1	1	0
	Faulty nipple development	-	0	0	1	1	0	
720	Number of dams	10	10	9	9	9	9	
	Normal	10	10	9	9	9	9	

Table 56 General signs of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	mg/kg	Number of pups and general signs	Days of lactation				
			0	1	2	3	4
Control	0	Number of pups	151	148	148	147	147
		Normal	148	148	147	147	147
		Death	3	0	1	0	0
1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene	45	Number of pups	161	159	158	157	156
		Normal	159	158	157	156	155
		Death	2	1	1	1	1
	180	Number of pups	156	156	156	155	153
		Normal	156	156	141	141	141
		Hypothermia	0	0	14	12	0
	720	Number of pups	80	72	70	70	70
		Normal	72	70	70	70	70
		Death	8	2	0	0	0

Table 57 Body weights of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group mg/kg	Control		1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene			
	0		45	180	720	
Number of dams	11		12	11	10	
Male weight						
Days of lactation						
0	6.7 ± 0.4		6.7 ± 0.7	6.7 ± 0.4	7.4 ± 0.5 **	
4	10.6 ± 1.1		10.9 ± 1.2	9.8 ± 0.8 (10)	12.2 ± 1.3 ** (9)	
Female weight						
Days of lactation						
0	6.4 ± 0.5		6.5 ± 0.8	6.3 ± 0.4	6.9 ± 0.5	
4	10.1 ± 1.3		10.5 ± 1.4	9.2 ± 0.9 (10)	11.4 ± 1.2 (9)	
Mean pups weight						
Days of lactation						
0	6.5 ± 0.4		6.6 ± 0.7	6.5 ± 0.4	7.2 ± 0.4 *	
4	10.3 ± 1.2		10.7 ± 1.3	9.5 ± 0.8 (10)	11.8 ± 1.2 * (9)	
Litter weight						
Days of lactation						
0	87.2 ± 11.2		87.1 ± 11.6	91.6 ± 7.3	52.2 ± 26.9 *	
4	136.1 ± 16.2		136.2 ± 15.3	133.7 ± 12.5 (10)	89.8 ± 34.0 * (9)	

Each value shows mean (g) ± S.D. per dam.

Significantly different from control group (*: P<0.05, **: P<0.01).

Figures in parentheses indicate number of dams.

Table 58 Necropsy findings of dead pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	Control	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene		
		45	180	720
mg/kg	0	45	180	720
Number of dams	2	2	2	2
Number of dead pups	2	3	13	3
Normal	2	3	13	3
Abnormal	0	0	0	0

Table 59 Necropsy findings of pups (F₁) in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration

Group	Control	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene		
		45	180	720
mg/kg	0	45	180	720
Number of dams	11	12	10	9
Number of male pups	68	71	66	30
Normal	68	71	66	30
Abnormal	0	0	0	0
Number of dams	11	12	10	9
Number of female pups	79	84	75	40
Normal	79	84	75	40
Abnormal	0	0	0	0

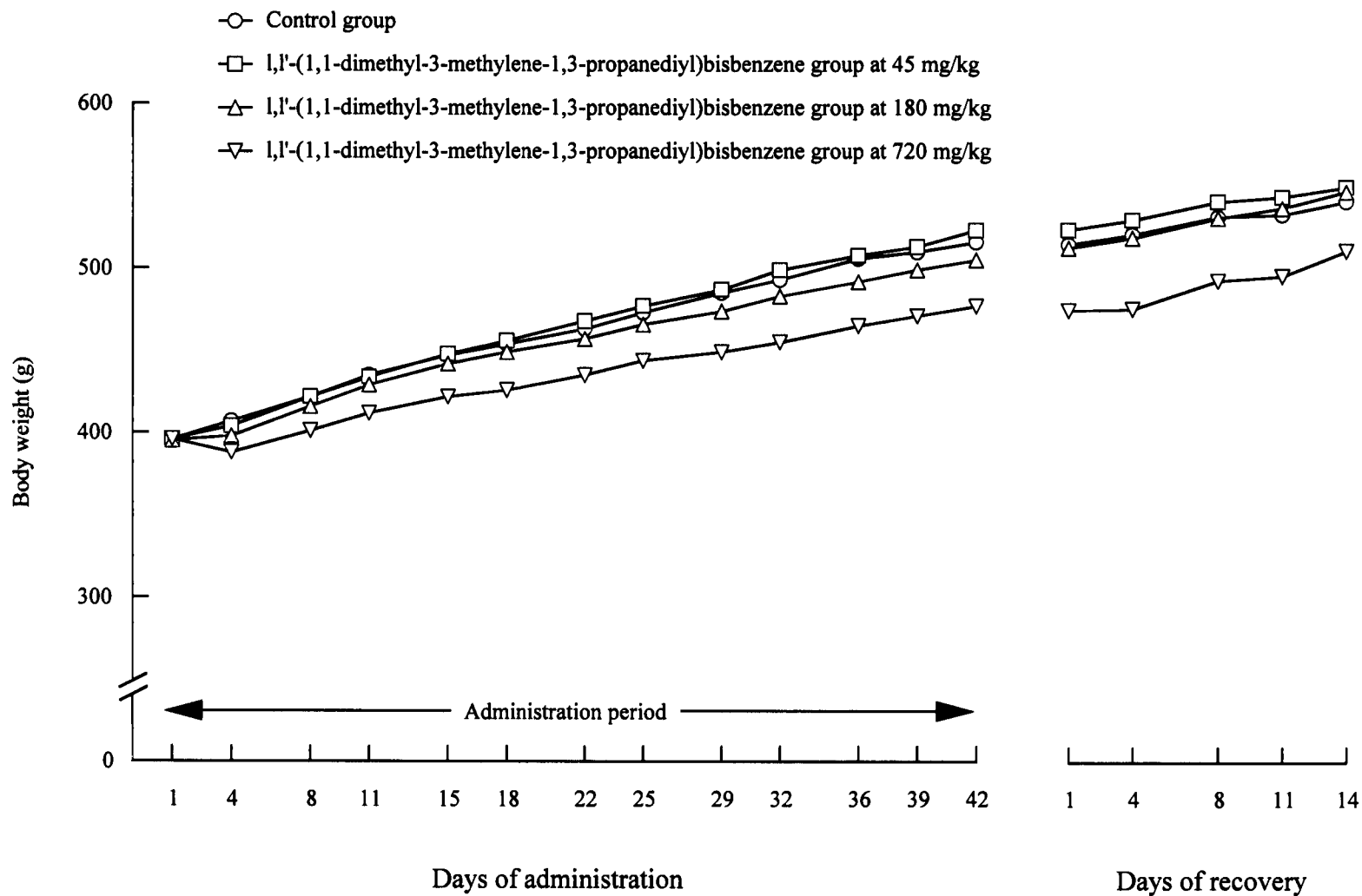


Fig. 2 Body weights of male rats in combined repeat dose and reproductive/developmental toxicity screening test of 1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene by oral administration